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CHANGES IN FIBRINOLYTIC ACTIVITY OF BLOOD AFTER PROSTATECTOMY

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Abstract : After prostatectomy, hypofibrinogenemia and bleeding were reported earlier. The objective of present study is to find out, of blood, after prostatectomy. Blood samples of patients posted for operations were studied by following tests before and after operation along with controls.

1. Euglobulin lysis time.
2. Plasminogen assay.
3. Fibrinogen estimation.

The results showed clearly that there is decrease in euglobulin lysis time indicating increased plasminogen activator level, increased plasminogen level and decreased fibrinogen level after the operation. This suggests that there is significant increase in fibrinolytic activity of blood after prostatectomy leading to hypofibrinogenemia and clotting defects.

Key words : prostatectomy, plasmin, fibrinogen, euglobulin lysis time, plasminogen assay, hypofibrinogenemia, fibrinolytic activity

INTRODUCTION

Bleeding disorders were reported in Abruptio-placentae, Prostatectomy, Cirrhosis of liver and Lobectomy of Lung. These were grouped under Defibrination syndromes. After Prostatectomy operations hemorrhages were reported over the years by many (2, 6, 7, 18). The hemorrhage was attributed to hypofibrinogenemia in these cases. As to the genesis of hypofibrinogenemia and bleeding there were mainly two hypothesis that were put forwarded.

According to one hypothesis by Williams EC, Mosher DF et al. and other (1, 2, 3, 4, 6, 15, 17, 22), Hypofibriinogenemia was caused by Disséminated Intravascular Clotting followed by increased Fibrinolytic activity. Williams EC and others (5, 7, 12, 18, 23, 24) observed that there is decreased fibrinogen, decreased platelet count and consumption of blood clotting factors.

The mechanism of DIC (Disseminated intervascular clotting) leading to increased Fibrinolysis (secondary) and bleeding is triggered by certain factors; trauma of

surgery (18, 19, 25) and carcinogenesis-Ca prostate (7, 21). There is a certain element of ischaemia and tissue hypoxia due to intravascular clotting leading to hypotension. All these can activate DIC through:

a) Extrinsic coagulation system by Tissue factor expressed on cell surfaces.

b) Intrinsic pathway by causing injury to endothelial cells-activation of XIIth factor.

c) Activation of all coagulation factors eg: factor X can be activated by cancer cells (7, 21).

All these lead to thrombin generation that in the presence of failure of control mechanisms (4, 5, 12, 20) results in intravascular clotting. This leads to thrombosis and to consumption of platelets, fibrinogen and other clotting factors. Simultaneously the activation of factor XII or fragments of factor XII, certain kininogens and damaged tissue and endothelial cells will have already activated the secretion of Tissue plasminogen activators (13) – contact activation system. The kidney is rich in another plasminogen activator i.e. Urokinase (1). All these activators along with their inhibitors, plasminogen and its inhibitors are adsorbed on to fibrin clot. Here the plasminogen is protected from the inhibitors and gets activated into plasmin (2). Thrombin also helps in the conversion of plasminogen into plasmin (27). The plasminogen activator inhibitor level and antiplasmin activity seems to be decreased in some cases (2, 5, 8, 18). The plasmin released will further lyse the fibrin clot. This result in hypofibrinogenemia and a fall in other clotting factors. The plasmin can digest fibrinogen directly and worsen the condition. The fibrin/fibrinogen degradation products (FDP) seems to potentiate the tissue plasminogen activator to induce more plasmin formation and they do have a anticoagulant property (20, 30).

Another group comprising of Booth N, Bennett B and others (6, 7, 11, 14, 16, 26) believed that bleeding after Prostatectomy could be due to Primary Fibrinolysis i.e. with or without DIC. Here the plasmin attacks directly fibrinogen and other clotting factors like V, VIII etc resulting in clotting defects that leads to hemorrhage due to hypofibrinogenemia and anticoagulant action of FDPs on fibrin monomers. The prostate is rich not only in tissue plasminogen activators but also in plasmin. In hyperplasia and carcinoma of prostate, plasminogen and its activators level may be more (8). The plasmin released into the blood during operation causes digestion of fibrin and fibrinogen together resulting in coagulation defects (14, 16, 26). Booth N, Bennett B et al. showed that there is disbalance in the plasmin-antiplasmin complexes in bleeding disorders characterised by Primary fibrinolysis.

Thus it is known since many years that Prostatectomy is followed by bleeding disorder. Therefore the objective of present study was to know whether there is increased fibrinolytic activity associated with hypofibrinogenemia after prostatectomy. If there is increased fibrinolytic activity, what is it due to and

what is the role of prostate in this bleeding disorder ?

METHODS

1) EUGLOBULIN LYSIS TIME (28)

2) PLASMINOGEN ASSAY (9)

3) FIBRINOGEN ESTIMATION (29)

Selection of cases :

About 46 patients aged about 60–70 yrs of enlarged prostate admitted for prostatectomy in Government Wenlock Hospital, Mangalore, were selected. They were devided into two groups. Group I of 29 cases had moderately enlarged prostate and Group II of 17 cases had large prostates. Both groups of patients blood samples were tested for Euglobulin Lysis Time (in minutes) before and after operation. In 5 cases of group II patients, Plasminogen assay and Fibrinogen Estimation were carried out before and after operation.

About 22 controls selected were normal healthy subjects of 60–70 yrs of age. Their blood samples were tested for Euglobulin Lysis Time. In 5 of the controls Plasminogen assay and Fibrinogen estimation (in gms%) were done. The units of measurements of Plasminogen assay were arbitrary values where 0.016 mg of Tyrosine was taken as 1 plasminogen unit.

Ideally each patient should have served as his own control. But I have taken normal persons of the same age group as controls to compare their fibrinolytic activity with that of prostatectomy patients before operation. This has given me an additional insight as to whether there is already some change in the fibrinolytic activity of the blood of the patient before the operation. Thus I wanted to compare both the control and the preoperative blood with that of the post operative sample.

RESULTS

The results of Euglobulin Lysis Time which indicate plasminogen activator level, showed decrease in time significantly in both groups of patients after prostatectomy when compared with preoperative as well

TABLE I

Test	*Control Mean±SD*	*Pre-operative Mean±SD*	*Post-operative Mean±SD*
Euglobulin Lysis Time (in minutes) Group I	177.4±25.52	154.034±36.24	150.931±35.99$$**
Group II	177.4±25.51	167.35±30.11	106.176±44.04$$$**
Plasminogen assay in Units	0.6±0.25	0.66±0.055	3.11±1.41$$**
Fibrinogen estimation (gm%)	0.264±0.038	3.264±0.0297	0.184±0.0518$***

"*"-Comparison of preoperative blood with post operative;
"$"-Comparison of control blood with post operative;
"*" or "$"= P<0.05; "**" or "$$" = P<0.01; "***" or "$$$" = P<0.001.

as control samples. This suggests a significant ($t = <0.001$). That resulted in hastening of clot lysis.

The plasminogen assay and fibrinogen estimation results also showed significant changes ($t = <0.01$). The plasminogen level increased after operation when compared with preoperative and control samples. The fibrinogen level showed significant decrease post operatively when compared with the preoperative and the control. This indicated that there is release of excess of activators which converted the plasminogen into plasmin. The resultant increased fibrinolysis is associated with hypofibrinogenemia.

DISCUSSION

Hypofibrinogenemia followed by bleeding disorder was known to occur in prostatectomy cases (2, 6, 7, 18). Therefore it was included as one of examples of Defibrination syndromes. The results of the present study concurs with it. As to the genesis of hypofibrinogenemia and hemorrhage mainly two hypothesis were putforwarded i.e. Primary fibrinolysis with or without DIC (Disseminated Intravascular clotting) and secondary fibrinolysis which is mainly due to DIC.

According to Williams EC, Mosher DF et al. and others (1, 2, 3, 4, 15, 22) hypofibrinogenemia was caused by DIC of small blood vessels, blocking them extensively to be followed by increased fibrinolytic activity-secondary fibrinolysis. Williams EC and others (5, 12, 18, 23, 24) all observed that there is decreased fibrinogen level, decreased platelet count and consumption of blood clotting factors leading to bleeding.

The mechanism of DIC in prostatectomy is triggered by trauma of surgery (18, 19, 25), element of ischaemia, hypoxia due to microthombi blocking vessels leading to hypotension. There is activation of both extrinsic and intrinsic pathway of blood coagulation. All these lead to thrombin generation that in the presence of failure of the controlling mechanism (4, 5, 12, 20) results in extensive clotting intravascularly. There is consumption of platelets, fibrinogen and other clotting factors. The activation of faXII leads to activation of secretion of Tissue Plasminogen activators (TPA)-contact activation system (13). These activators, plasminogen and their inhibitors all are adsorbed on to fibrin clot. The plasminogen is converted to plasmin, lyses the fibrin and other clotting factors leading to hypofibrinogenemia and bleeding disorders. The Fibrin/fibrinogen degradation products seem to potentiate the tissue plasminogen activator to induce more plasmin formation and they do have a anticoagulant property by interfering with polymerisation of fibrin (20, 30). The plasminogen activator inhibiter level and antiplasmin activity of blood seem to be decreased in DIC (2, 5, 8, 18).

Another group comprising of Booth N, Bennett B and others (6, 7, 8, 11) believed that bleeding after prostatectomy could be due to Primary fibrinolysis i.e. with or without DIC. In hyperplasia that too in Adenocarcinoma of prostate, there is increase in plasminogen activators and plasmin content (8, 10) which may be released into the blood stream during operation. This directly attacks fibrin/ fibrinogen and other clotting factors like V, VIII etc resulting in clotting defect (14, 16, 20). Booth N, Bennett B et al showed that there is disbalance in the plasmin-

antiplasmin complexes in bleeding disorders characterised by primary fibrinolysis.

In carcinoma of prostate gland the mechanism of Primary fibrinolysis is brought about by DIC in the following way (7, 8, 26).

a) Tissue factor present in cancer cells and protease present in mucin secreted by Adenocarcinoma both activate fa X (22).

b) Tissue factor produced by monocyte due to interaction with antigens and adhesion and activation by platelets produces.

c) Extra vascular clotting and fibrin deposition by cancer cells and tissues. When these procoagulants are excessive there is imbalance of procaogulants-anticogulants resulting in increased plasmin release which may attack fibrinogen/ fibrin and other clotting factors (18) producing hypofibrinogenemia and bleeding disorder.

I feel that both these hypothesis may be true as far as the present study of prostatectomy is concerned. Because the results clearly showed an increase in fibrinolytic activity of blood where there was increase in plasminogen activator level as well as increase in plasminogen level which could be due to DIC or carcinomatous changes in some of the prostate gland. The follow up of histopathological report of 3 prostatectomy cases of II group revealed adenocarcinomatous changes in prostate and one of them died due to post operative hemorrhage. The observations in my study also showed hypofibrinogenemia which was due to increased fibrinolytic activity. As to prove whether it is due to primary or secondary fibrinolysis we have to estimate fibrinogen and fibrin degradation products. Presently this is beyond the scope and facility available in our department.

CONCLUSION

The hypofibrinogenemia associated with bleeding disorder after prostatectomy operation could be due to:

a) Depletion of clotting factors.

b) Anticoagulant effect of FDP.

c) By further decrease in fibrinogen, V, VIII due to the plasmin digestion of them if generated in excess of antiplasmin activity which itself is decreased or by secondary fibrinolysis.

Therefore, it is advisable to make use of appropriate antifibrinolysin agents during prostatectomy operation as Sharifi R, Lee M, Ray P. et al. have demonstrated to prevent an impending bleeding disaster due to increased fibrinolytic activity of blood after prostatectomy.

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